Prospective Study of Simultaneous Orthoiodohippurate and Diethylenetriaminepentaacetic Acid Captopril Renography

The Einstein/Cornell Collaborative Hypertension Group—M. Donald Blaufox (Chairman, Steering Committee), Eugene J. Fine, Sherman Heller, James Hurley, Marcy Jagust, Yi Li, Samuel J. Mann, Thomas G. Pickering, Patrick Zanzonico and Cheng-Gang Zhang

Members of the Writing Committee—Eugene J. Fine (Chairman), M. Donald Blaufox, Yi Li and Samuel J. Mann

Department of Nuclear Medicine, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx; and Departments of Medicine, Nuclear Medicine and Radiology, New York Hospital/Cornell University Medical Center, New York, New York

Captopril renography (CR) has been established in the past 10 yr as a useful diagnostic test for renovascular hypertension. However, direct comparison of tubular and glomerular tracers, quantitative criteria, comparison of quantitative and qualitative results and the reliability of the results in renal failure have not been described in a systematic, prospective fashion. **Methods:** Same-day baseline and CR using ^{99m}Tc-labeled diethylenetriaminepentaacetic acid (DTPA) and [^{131}I]orthoiodohippurate (OIH) were simultaneously performed in two groups of hypertensive subjects, one with demographically defined essential hypertension (n = 43) and the other (n = 60) with a high prevalence of renovascular disease, defined with angiograms. Quantitative criteria for abnormal CR were derived from results among the subjects with essential hypertension. Qualitative analysis was performed using widely established criteria. **Results:** There were no statistically significant differences between quantitative and qualitative accuracy, between OIH and DTPA or among quantitative parameters. The best accuracies for quantitative CR were 56% with DTPA (n = 57) and 60% with OIH (n = 60), in both cases using the relative renal uptake parameter. Qualitative CR (n = 60) had accuracies of 43% (DTPA) and 50% (OIH), both hindered by 29 (DTPA) and 25 (OIH) abnormal but nondiagnostic studies. Two false-positive studies were detected. Twenty-seven of 29 nondiagnostic studies were associated with a glomerular filtration rate of <50 ml/min (n = 17), one small kidney (n = 17) and/or bilateral renal artery stenosis (n = 16). Supplemental measurement of in vitro stimulated plasma renin activity insignificantly ($p > 0.10$) and improved accuracies to 63% (DTPA) and 70% (OIH), without introducing additional false-positive tests. **Conclusion:** Orthoiodohippurate and DTPA have comparable accuracy in prospective simultaneous evaluation of CR. False-positive studies are fewer than 5%. The accuracies of quantitative and qualitative criteria do not differ significantly but may be improved by supplemental use of the in vitro stimulated plasma renin activity. In individuals with renal insufficiency, small kidneys and/or bilateral renal artery disease, up to 48% of CR studies are abnormal but nondiagnostic.

Key Words: captopril renography; renovascular hypertension; renal insufficiency

J Nucl Med 1998; 39:522–528

Captopril renography (CR) has been established in the past 10 yr as an effective diagnostic tool in the evaluation of hypertensive patients for renovascular hypertension. Important questions regarding methodology, clinical utility and accuracy of CR have been addressed in numerous, principally retrospective studies (*1–7*), involving multiple, sometimes changing protocols. The Einstein/Cornell Collaborative Study was designed to evaluate CR prospectively (*8*) with a unified protocol. This investigation addressed the need for carefully controlled methodology in all subjects, with attention to salt and water balance, and simultaneous evaluation of a tubular [orthoiodohippurate (OIH)] and a glomerular [diethylenetriaminepentaacetic acid (DTPA)] tracer, which have not been adequately studied.

MATERIALS AND METHODS

Patient Selection

This study examined two groups of hypertensive subjects: one with a very low (Group I) and the other with a high (Group II) prevalence of renovascular hypertension. A population similar to Group I was well characterized in the Hypertension Detection and Follow-up Program as having a prevalence of renovascular hypertension of <1% (*9*).

Objectives in the Group I population included determining the range of physiologic and renographic responses of tubular and glomerular tracers to captopril in subjects, thus, characterized demographically as having essential hypertension and determining false-positive and true-negative rates of CR in this group using simultaneous DTPA and OIH. These data then were used to determine quantitative physiologic and renographic criteria for positive and negative studies.

Group II consisted of subjects referred to the hypertension unit of the Cornell University Medical Center with a high (>30%) likelihood of renovascular hypertension (RVH). Objectives in this group included assessment of the true-positive and false-negative rates of qualitative renography using tubular and glomerular tracers in subjects with a higher prevalence of RVH and evaluation of quantitative renography for evaluation of RVH, using the criteria established from Group I data.

Specifics of Selection Criteria

Group I. Forty-three volunteers (27 men, 16 women) were recruited, with informed consent, from an ongoing evaluation (Trial of Antihypertensive Interventions and Management) of patients with mild hypertension (*10*). These patients had a diastolic blood pressure (BP) of 90 mmHg–100 mmHg without clinical evidence for significant end-organ damage, i.e., a serum creatinine concentration of <1.9 mg/dl, normal urinalysis and the absence of grade III or IV retinopathy or left ventricular hypertrophy.

Group II. Eighty-four subjects (37 men, 47 women) were recruited from referral to Cornell University Medical Center with clinical evidence suggesting a higher likelihood for renovascular disease. The clinical characteristics in this group included: severe diastolic hypertension, end-organ damage, abdominal and flank

Received Jan. 3, 1997; revision accepted Jun. 24, 1997.

For correspondence or reprints contact: Eugene J. Fine, MD, Department of Nuclear Medicine, Jacobi Medical Center, BN13, Pelham Parkway and Eastchester Road, Bronx, NY 10461.

bruits and prior evidence of a small kidney. Some of these subjects had prior angiographic evidence for renal artery stenosis (RAS); they were to undergo repeat angiography.

Subjects with serious intercurrent illness, such as malignancy, anemia, bleeding disorders, major organ disease or other conditions likely to interfere with adherence to the intervention protocol were excluded.

Patient Preparation (All Subjects)

Antihypertensive medications were discontinued, consistent with safe medical practice. Continuance of medications was noted when required. In all subjects, diuretics and enalapril were discontinued for at least 1 wk, and captopril was discontinued 4 days before study. A no-added-salt diet of 2g–4g per day was prescribed, representing an increase in salt for those already on severe salt restriction and a decrease for others. A 12-hr urine sample was collected for creatinine clearance determination.

Subjects were instructed to eat a breakfast of juice, decaffeinated beverage and dry toast to minimize differences in renal function induced by variations in diet.

On the morning of the exam, a urine specimen was obtained for specific gravity. Two-hundred fifty milliliters of fluid were administered orally before the first renogram if the specific gravity was >1.015. Intravenous lines in both arms were used for separate access to blood sampling and tracer administration. Fluid was administered again before the second renogram in all subjects (250 ml).

Pre-Captopril Study (All Subjects)

Baseline Acquisition and Data Collection. Studies were acquired in supine position using a large field-of-view camera and medium-energy collimator. The field of view included kidneys and heart for determination of mean transit time (MTT). Orthoiodohippurate (150 μCi ^{131}I) was followed at 3 min by injection of 5 mCi ^{99m}Tc-DTPA. Three-second computer frames were obtained for 8-min and 30-sec frames for 22 additional min, in a 64 × 64 word matrix. Energy windows centered at 364 KeV and 140 KeV permitted dual-tracer acquisition.

Renographic parameters measured with both tracers included relative renal uptake (RU), time to peak (Tpk) and renographic retention parameters [20 min/peak (Pk)] and 30 min/Pk. Mean transit time was measured from the DTPA data.

Technetium-99m-DTPA activity measured in blood samples at 45 min and 1 hr 45 min was used to assess glomerular filtration rate by the two-sample method (*11*). The 45-min sample was used for the single-sample method of determining effective renal plasma flow (ERPF) using OIH (*12*).

Post-Captopril Study (All Subjects)

At 2 hr, a blood specimen was obtained for the baseline plasma renin activity (PRA), and a crushed 25-mg captopril tablet was administered with 250 ml of water. Blood pressure was monitored for 1 hr, after which blood samples were obtained for stimulated PRA. The baseline and stimulated PRA constituted a "captopril test," scored by the criteria of Muller et al. (*13*). Repeat renography was performed using double the initial DTPA and OIH activities. Repeat glomerular filtration rate (GFR) values and ERPF values were obtained using the initial methodology after subtracting appropriate background activity. Technical details were described previously (*8,14*).

Angiography was performed in 60 of the 84 Group II subjects. Renal artery stenosis was defined as a luminal narrowing of >50%. Renovascular hypertension was defined by clinical follow-up (detailed below).

Qualitative Analysis (All Subjects)

Qualitative renography was assessed independently by two of the investigators, both experienced nuclear medicine physicians, who were blinded to patient group or clinical status, using an adaptation of the criteria of Nally et al. (*15*). Using these criteria, a worsening in the renogram grade post-captopril was considered positive for RVH, except for minor prolongation of Tpk in an otherwise normal renographic study. Other investigators have reported that bilateral symmetric worsening in renographic grade is not usually diagnostic for RVH (*6*). From the first 26 Group I subjects, the following additional abnormal but nondiagnostic (abnormal-ND) categories were defined:

1. An abnormal baseline renogram without change after captopril; and
2. Worsening of renographic grade considered due to pelvic retention post-captopril, particularly if cortical post-captopril renograms were normal.

Quantitative Analysis

The mean differences between post- and pre-captopril values for renographic parameters from hypertensive Group I subjects and the s.d. of these differences were obtained. In instances in which the direction of captopril induced physiologic change is already known (for example, prolongation of 20 min/Pk, 30 min/Pk, Tpk and MTT or reduced uptake), one-tailed limits for change were used, requiring a change of 1.645 s.d. to define a 95% confidence limit and 1.34 s.d. to define a 90% confidence limit. Abnormal was defined to lie outside these ranges.

A clearly abnormal DTPA renogram characterized by a blood pool disappearance curve does not lend itself to the above type of analysis for the retention parameters. The disappearance rate depends on the function of the contralateral kidney, so quantitative criteria for 20 min/Pk, 30 min/Pk and MTT have no relevant physiologic significance. Renograms in this category were considered ineligible for evaluation by quantitative criteria and were judged abnormal by inspection.

Statistical Methods (All Subjects)

Pre- versus post-captopril comparisons were made by paired nonparametric testing (Wilcoxon), in which a subject or kidney could be used as its own control. Nonparametric group testing (Mann–Whitney U) and pooled Student's t-test were used in cases for which group comparisons were more appropriate. Contingency tables of true-positive, true-negative, false-positive and false-negative were evaluated by chi-square analysis. Comparisons between contingency tables were performed by calculating chi-square heterogeneity (*16*).

Selection of Subjects for Angiography

Group I subjects were presumed to have essential hypertension. An obviously abnormal captopril renogram in Group I, nevertheless, would trigger further evaluation, including angiography, if necessary. Criteria for CR, previously reported (*14*) from the first 26 Group I subjects, were used to determine the need for angiography in all subsequent Group I subjects.

All Cornell University Medical Center (CUMC) (Group II) subjects were eligible for angiography.

Criteria for Renal Artery Stenosis and Renovascular Hypertension: Angiographic and Follow-Up of Percutaneous Transluminal Angioplasty

All intra-arterial digital subtraction angiography was performed at the CUMC. Stenotic lesions were graded by a radiologist who was blinded to the results of the captopril renogram and reported as percentage luminal stenosis. Fifty percent or more luminal stenosis was considered positive for significant RAS.

TABLE 1
Baseline Physiologic Data

	Group I	Group II
Age (yr)	59 ± 9	54 ± 18
BUN (mg/dl)	16 ± 5*	25 ± 16*
Creatinine (mg/dl)	1.0 ± 0.2*	1.6 ± 1.3*
Systolic blood pressure (mmHg)	141 ± 16*	170 ± 33*
Diastolic blood pressure (mmHg)	85 ± 8*	99 ± 13*
Creatinine clearance (ml/min)	119 ± 49*	80 ± 36*

*$p < 0.01$.
Results are reported in mean ± s.d.

Captopril renography results in Group II subjects were determined to be correct or incorrect by comparison to the results of angiography, which were taken as the standard.

Subjects with arterial stenoses of 50% or greater were eligible, in principle, for percutaneous transluminal angioplasty (PTCA). Stenotic lesions of excessive length or with calcium deposition were not good candidates for angioplasty. Follow-up of medications and BP was attempted in all subjects. For subjects who were followed at least 6 mo after the procedure, the following criteria were used to judge the success of PTCA:

1. Cure: reduction of systolic BP to <140 mmHg and diastolic BP to <90 mmHg without antihypertensive medication;
2. Improvement: reduced BP (systolic by at least 15 mmHg and diastolic by at least 10 mmHg) on the same number of antihypertensive medications or no change in BP on fewer antihypertensive medications;
3. No change or worsening: follow-up BPs not meeting above requirements.

A true-positive or false-negative captopril renogram was characterized by cure or improvement in BP control after PTCA. A true-negative or false-positive study was characterized by no change or worsening of BP control after PTCA.

Other Features of Study Methodology

All data from the CUMC and the Albert Einstein College of Medicine (AECOM) were collected on identical computer equipment. Radionuclide scintirenography data were processed centrally at AECOM after transfer from floppy disks. Demographic data were entered in a uniform database distributed to both CUMC and AECOM and then into a centralized database.

RESULTS

Among Group I subjects, one was excluded from final analysis because of a solitary kidney, leaving 42 for analysis. Among 84 Group II subjects, 7 were excluded due to incomplete renographic data or technical failure; 11 refused angiography; 5 had PTCA after angiography but before CR; and 1 angiogram was noninterpretable. Therefore, 60 Group II subjects were eligible for complete data analysis. Baseline data for all subjects, shown in Table 1, indicate higher serum creatinine and mean BP in Group II subjects.

TABLE 2
Results of Qualitative Captopril Renography (Group II)

	Angiogram	
	+	−
DTPA		
+	14	2
−	3	12
Abnormal-ND	24	5
OIH		
+	18	2
−	3	12
Abnormal-ND	21	4

TABLE 3
Captopril Test* (Group II)

	Angiogram	
	+	−
Captopril test		
+	21	3
−	21	12

*Criteria of Muller et al. (*13*).

Qualitative Results

Group I Subjects. None of the subjects had renograms that were interpreted as positive for RVH with either OIH or DPTA. Therefore, none of the Group I subjects underwent angiography.

With DTPA, pelvic retention was seen post-captopril in eight subjects, two unilaterally and six bilaterally. In five, cortical renograms had a normal appearance. In the remaining three, cortical renograms showed modestly prolonged excretion after captopril. None of these eight subjects had a positive PRA response to captopril, and none were interpreted as positive responses for RVH.

Two OIH scintigrams, with a minor degree of pelvic retention after captopril, demonstrated normal whole-kidney and cortical renogram curves.

Group II Subjects. Among Group II subjects (n = 60), 23 had bilateral RAS, 20 had unilateral disease and 17 had no renal artery disease or <50% luminal narrowing.

Captopril renography and angiography were compared (Table 2) for DTPA and OIH. There were 26 correctly identified studies with DTPA (14 true-positive and 12 true-negative) and 30 correctly identified with OIH (18 true-positive and 12 true-negative). Both tracers had equal numbers of false-negatives (three) and false-positives (two). There were 29 abnormal-ND (see Materials and Methods) examinations with DTPA and 25 with OIH.

The plasma renin captopril test (Table 3, n = 57) yielded 21 true-positive exams, 12 true-negatives, 21 false-negatives and 3 false-positives.

The captopril test, when applied to the abnormal-ND exams, improved true-positive and true-negative rates without introducing false-positive results, but more false-negatives were introduced (Table 4).

Correct results using OIH were obtained more frequently in subjects with higher levels of renal function (Fig. 1 and Table 5). Abnormal-ND results were more likely in patients with GFR values of <50 ml/min. The mean GFR was higher (94 ± 40

TABLE 4
Captopril Renography and Captopril Test (Group II)

	Angiogram	
	+	−
DTPA		
+	22	2
−	20	16
OIH		
+	25	2
−	16	17

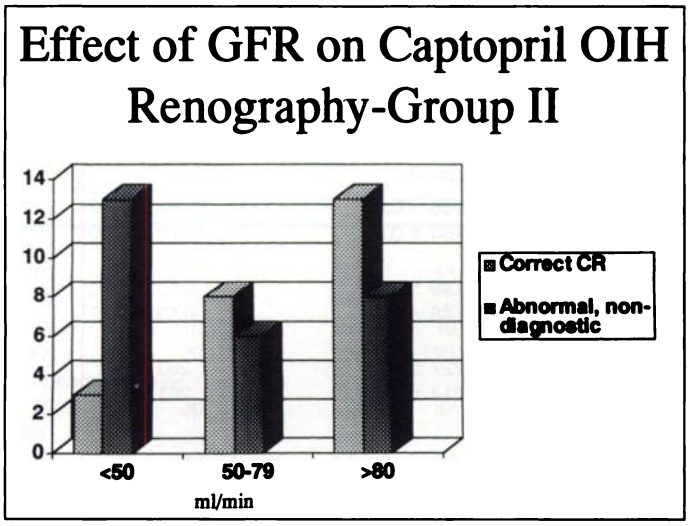

FIGURE 1. The best GFR values are associated with the most correct OIH captopril renograms, whereas the lowest values of GFR are seen with the fewest correct studies and the most abnormal-ND exams. Intermediate values of GFR have an intermediate number of correct captopril renograms.

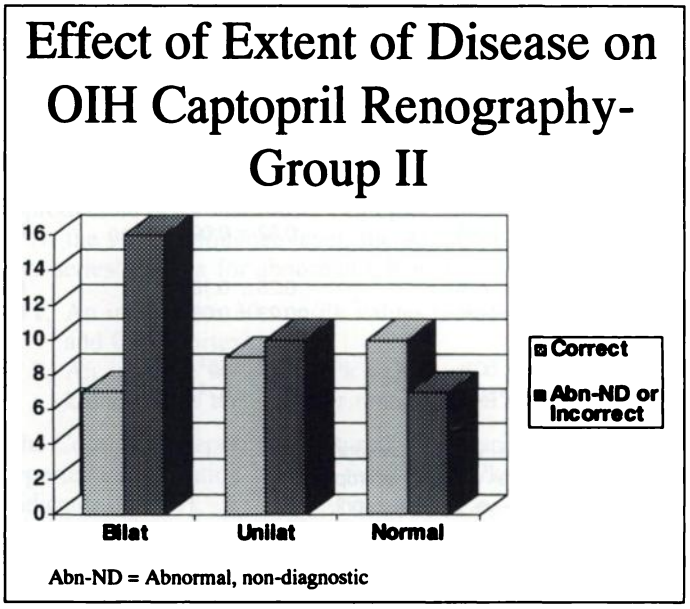

FIGURE 2. The extent of renovascular disease is correlated with the results of CR. Bilateral RAS is associated with the highest number of abnormal-ND or incorrect OIH captopril renograms and the fewest correct studies. Conversely, subjects with normal renal arteries have the most normal captopril renogram studies and the fewest number of abnormal-ND or incorrect exams. Individuals with unilateral disease have intermediate numbers of correct captopril renograms and intermediate numbers of abnormal-ND or incorrect studies.

ml/min, $p < 0.05$) in correctly identified subjects than it was in those with abnormal-ND or incorrect exams (GFR = 73 ± 36 ml/min). Mean blood urea nitrogen (BUN) (20 ± 9 mg/dl, n = 30) was lower ($p < 0.05$) in correctly identified subjects than it was in abnormal-ND or incorrectly identified subjects (BUN = 31 ± 16 mg/dl, n = 29).

The extent of vascular involvement also influenced accuracy of results (Fig. 2). Abnormal-ND or incorrect results were most likely with bilateral RAS, of intermediate likelihood with unilateral disease, and least likely with normal renal arteries. The likelihood of correct results obtained by OIH CR increased with decreasing extent of disease.

Quantitative Results

Group I. In Table 6, the response of physiologic parameters to captopril demonstrates no significant difference in GFR before and after captopril. ERPF increased slightly from 433 ± 116 ml/min to 463 ± 138 ml/min ($p = 0.05$). Plasma renin activity increased from 1.6 ± 1.2 ng/ml/hr to 3.0 ± 4.7 ng/ml/hr ($p < 0.01$), and BP fell after captopril. Very mildly asymmetric renal uptake improved toward greater symmetry after captopril administration.

Renogram retention parameters are indicated in Table 7 for whole-kidney values. For OIH, there were no significant captopril-induced changes for 20 min/Pk or 30 min/Pk in either kidney. However, small but significant increases were noted after captopril for Tpk using OIH and for all DTPA retention parameters. The kidney with more than 50% function did not behave differently from the lesser functioning kidney for any parameter.

Quantitative criteria for abnormal CR with 90% and 95% confidence limits for post- minus pre-captopril values are shown in Table 8, derived from Group I subjects. There were no statistically significant differences detected between the kidneys in Table 7, so in Table 8, the expected changes for subjects are pooled for all kidneys.

For OIH, at 90% confidence limits, whole-kidney values of Tpk after captopril must increase by ≥199 sec (238 sec at the 95% confidence level) to be considered abnormal. Cortical prolongations must be ≥102 sec (127 sec, 95% level). Values for 20 min/Pk must increase ≥0.17 for whole-kidney regions of interest (ROIs) (0.22, 95% level) and 0.14 cortically (0.19, 95% level). Values for 30 min/Pk prolongations must be ≥0.13 for whole-kidney regions (0.16, 95% level) and ≥ 0.12 for renal cortical ROIs (0.15, 95% confidence level). Corresponding values for DTPA are displayed.

Relative renal uptake (whole kidney) of DTPA or OIH must decrease by 2% or more (90% confidence level) after captopril to be considered abnormal (3% decrease, 95% confidence level).

Group II. The accuracies of whole-kidney CR are displayed in Table 9, including quantitative and qualitative results, for comparison. Quantitative CR results are derived from renogram

TABLE 5
Hippuran Data (Group II Subjects)

	BUN (mg/dl)	Creatinine (mg/dl)	GFR (ml/min)
Correct (n = 30)	20 ± 9	1.2 ± 0.4	94 ± 40
Abnormal-ND or incorrect (n = 30)	31 ± 16	2.0 ± 1.2	73 ± 36
p	<0.01	<0.01	<0.05

Results are reported in mean ± s.d.

TABLE 6
Response to Captopril (Group I Subjects)

	Pre-captopril	Post-captopril	p
GFR (ml/min)	116 ± 4.3	114 ± 4.9	0.08
ERPF (ml/min)	433 ± 17.8	463 ± 21.3	0.05
PRA (ng/ml/hr)	1.6 ± 0.2	3.0 ± 0.7	<0.01
Systolic BP (mmHg)	138 ± 2.3	124 ± 2.0	<0.0001
Diastolic BP (mmHg)	85 ± 1.1	79 ± 1.1	<0.0001
DTPA (RU in %)*	46.5 ± 0.6	46.7 ± 0.7	ns
OIH (RU in %)*	47.0 ± 0.7	47.5 ± 0.7	0.05

*RU (in %) by kidney with <50% renal function.
Results are reported in mean ± s.e.m.; ns = not significant.

TABLE 7
Renogram Retention Parameters: Pre- versus Post-Captopril Values (Group I)

	OIH		DTPA	
	Pre-captopril	Post-captopril	Pre-captopril	Post-captopril
20 min/Pk				
Kidney <50%	0.35 ± 0.10	0.36 ± 0.14	0.56 ± 0.09	0.62 ± 0.09*
Kidney >50%	0.32 ± 0.09	0.35 ± 0.14	0.54 ± 0.09*	0.60 ± 0.10*
30 min Pk				
Kidney <50%	0.25 ± 0.10	0.25 ± 0.12	0.49 ± 0.09†	0.55 ± 0.10†
Kidney >50%	0.23 ± 0.08	0.23 ± 0.11	0.48 ± 0.08†	0.53 ± 0.12†
Tpk (sec)				
Kidney <50%	215 ± 55‡	298 ± 149‡	227 ± 75‡	263 ± 69‡
Kidney >50%	208 ± 47§	257 ± 85§	214 ± 51§	261 ± 51§

*p = 0.0001, pre- vs. post-captopril.
†p < 0.0002, pre- vs. post-captropril.
‡p = 0.003, pre- vs. post-captopril.
§p < 0.001, pre- vs. post-captropril.
Kidney <50% = kidney with <50% renal function; Kidney >50% = kidney with >50% renal function.

parameter limits established in Table 8 (90% confidence limits displayed only). A positive study for Group II subjects, therefore, is one in which the change in a renogram parameter is greater than the 90% confidence limit established from Group I subjects in Table 8.

The best accuracy [(true-positive + true-negative)/total] for quantitative parameters (56%, n = 57 with three technical failures) for DTPA was obtained with the RU parameter. This was at the expense of two false-positive exams. For OIH, RU also performed with the highest measured accuracy (60%, n = 60) of the quantitative parameters. This occurred identically at criteria for both 90% and 95% confidence levels, but at the expense of seven false-positive exams at the 90% level; only three false-positive exams occurred at the 95% level (95% limits not displayed in Table 9). With OIH, an accuracy of 55% (n = 60) was obtained with only two false-positive exams, using the 20 min/Pk criterion at the 90% confidence level. Quantitative results derived from cortical ROIs were not statistically better or worse than those obtained from whole-kidney renography.

Qualitative CR had an accuracy of 50% (n = 60) for OIH, with two false-positive exams and 25 abnormal-ND studies. When the stimulated plasma renin test was used to adjudicate abnormal-ND studies (Table 4), the accuracy of OIH reached 70% (n = 60), with no new false-positives. The accuracy of qualitative DTPA renography was 43% (n = 60), with 29 abnormal-ND studies and two false-positives. Application of the captopril stimulated renin test to the abnormal-ND exams improved the accuracy to 63% (n = 60), with no additional false-positives. Strict quantitative rules for abnormal study detection, when applied in a blinded evaluation, therefore, offered no improvement over similarly blinded qualitative evaluation for either DTPA or OIH when supplemented by the results of the captopril stimulated plasma renin assay. There were no significant differences in Table 9 among or between all quantitative and qualitative methods.

Follow-Up Blood Pressure Data for Determination of Renovascular Hypertension

Forty-three Group II subjects had RAS. Twenty-eight underwent PTCA. Six-month follow-up data were available in 17, including four with bilateral disease who underwent unilateral

TABLE 8
Criteria for Quantitative Captopril Renography (Derived from Group I Data)

				Significant change at confidence level	
	Pre-captopril	Post-captopril	Post − Pre*	90%†	95%†
20 min/Pk					
OIH	0.33 ± 0.10	0.35 ± 0.14	0.02 ± 0.12	+0.17 (+0.14)	+0.22 (+0.19)
DTPA	0.55 ± 0.09	0.61 ± 0.10	0.06 ± 0.08	+0.16 (+0.20)	+0.19 (+0.25)
30 min/Pk					
OIH	0.24 ± 0.09	0.25 ± 0.11	0.01 ± 0.10	+0.13 (+0.12)	+0.16 (+0.15)
DTPA	0.48 ± 0.09	0.54 ± 0.11	0.06 ± 0.09	+0.18 (+0.18)	+0.21 (+0.22)
Tpk (sec)					
OIH	210 ± 51	277 ± 117	67 ± 105	+199 (+102)	+238 (+127)
DTPA	221 ± 63	262 ± 60	41 ± 68	+128 (+141)	+153 (+163)
RU (%)‡					
OIH	47.0 ± 4.8	47.5 ± 4.6	0.5 ± 1.9	−0.019	−0.028
DTPA	46.5 ± 4.2	46.7 ± 4.4	0.2 ± 1.8	−0.020	−0.028

*Post- pre represents the difference between pre- and post-captopril values mean ± s.d.
†Values in parentheses are derived from renal cortical data.
‡Represents percent of total renal function provided by the kidney with <50% total function.
Results are expressed in mean ± s.d.

TABLE 9
Captopril Renography: Quantitative Versus Qualitative Results (n = 60)

	Results using quantitative criteria*				Qualitative results	
	Tpk	20/Pk	30/Pk	Relative uptake (%)	Qual (−)	Qual w/PRA
DTPA						
TP	14	16	13	13	14	22
FP	1	4	1	2	2	2
TN	16	13	16	19	12	16
FN	29	27	30	23	3	20
Abnormal-ND					29	
TP + TN	30	29	29	32	26	38
OIH						
TP	12	16	17	20	18	25
FP	2	2	3	7	2	2
TN	17	17	16	15	12	17
FN	29	25	24	16	3	16
Abnormal-ND					25	
TP + TN	29	33	33	36	30	42

*90% confidence level using values derived from whole-kidney ROIs.

TP = true-positive; FP = false-positive; TN = true-negative; FN = false-negative; Qual = results of qualitative renography; Qual w/PRA = results of qualitative renography using results of stimulated PRA to adjudicate abnormal, non-diagnostic tests. Note: PRA resuls were unavailable in two subjects.

PTCA, in whom clinical diagnosis of RVH could not be adequately assessed.

Of the 13 evaluable subjects (7 with bilateral and 6 with unilateral disease) with either OIH or DTPA, there were 6 true-positive, 3 true-negative, 0 false-positive and 4 false-negative results. Three of four false-negative results were in subjects with bilateral disease.

DISCUSSION

Captopril renography has been established over the past 10 yr as a useful method of establishing the diagnosis of RVH. However, direct comparison of tubular and glomerular tracers, quantitative criteria, comparison of quantitative and qualitative results and the reliability of the results in renal failure have not been described in a systematic, prospective fashion. We report the results of our prospective study of CR. Unique features of the investigation include same-day baseline and CR using ^{99m}Tc-DTPA and ^{131}I-OIH simultaneously in two groups of hypertensive subjects, one with demographically defined essential hypertension (n = 43) and the other with a high prevalence of renovascular disease, all with angiograms (n = 60). The plasma renin captopril test was performed simultaneously. The study provides specific data comparing subjects with essential hypertension, the population of hypertensives from which one must distinguish renovascular disease, with a referred population with a high prevalence of renal dysfunction. The study also prospectively compares defined quantitative criteria of abnormal CR with qualitative analysis.

Among subjects with mild essential hypertension, the mean BP at the time of CR (i.e., off medications) was in the normal range, reflecting both well-controlled BP in this group and its slow rate of recidivism after discontinuation of medications. Total GFR and the percentage GFR contributed by each kidney were unchanged after captopril. Total ERPF increased an average of about 10%, a likely consequence of expected captopril-induced vasodilation. Very mild asymmetry of ERPF was noted, which was unlikely to be of physiologic importance. This asymmetry was lessened after captopril, possibly reflecting regression toward the mean. There was a small increase in PRA after captopril, as expected, and small but significant symmetric increases after captopril in 20 min/Pk values for DTPA and in Tpk and 30 min/Pk values for DTPA and OIH. Renal function in essential hypertension, therefore, was highly reproducible before and after captopril administration.

At the 90% confidence level, the AECOM/CUMC prospective series' criteria for abnormal CR with OIH were:

1. An increase in 30 min/Pk values of 0.13 (whole kidney) and 0.12 (cortex);
2. An increase in 20 min/Pk values of 0.17 using whole-kidney ROIs and 0.14 for renal cortical regions.

The Consensus Report on Captopril Renography (*17*) similarly reported prolongation of 0.15 for 20 min/Pk values to be an indicator of RVH.

Setaro et al. (*18*), using DTPA, found prolongation of Tpk by >11 min post-captopril to be their most accurate criterion for RVH. The Consensus Report (*17*) and Mann et al. (*6*), using MAG3 or OIH, required Tpk prolongation by >2 min post-captopril. Such discrepancies are unlikely due to tracer differences and more likely reflect different patient populations. In the present series, Tpk had to exceed 199 sec for whole-kidney ROIs and 102 sec for renal cortical regions to exclude essential hypertension with at least 90% confidence.

Our results demonstrated few false-positive exams, in agreement with prior literature (*1–7,17–19*). Our very high percentage of abnormal-ND exams by either quantitative or qualitative criteria appears to be related to subject selection. Our Group II population of referred hypertensives was notable for bilateral renal artery disease in 37% and GFR values of <50 ml/min in 27%. Of the 29 DTPA subjects with abnormal-ND captopril renograms, 17 had one small kidney with markedly reduced function, unchanged by captopril; 17 had GFR values of <50 ml/min or bilaterally flattened pre-captopril renogram curves; and 16 had bilateral RAS. Multiple factors combined in 27 of these 29 abnormal-ND studies. Although reduced renal function and bilateral disease increased the likelihood of false-negative or abnormal-ND results with OIH and DTPA, there were few false-positive exams.

Qualitative and quantitative CR did not differ statistically ($p > 0.05$). Qualitative OIH renography had an accuracy of 50% (n = 60) with two false-positive exams; this was hindered by 25 abnormal-ND studies. The use of the stimulated plasma renin test to adjudicate these abnormal studies improved accuracy to 70% (n = 60), the best value, although not significantly ($p > 0.05$), with no new false-positives. Qualitative DTPA renography had an accuracy of 43% (n = 60) with 29 abnormal-ND studies and two false-positives, improving to 63% (n = 60) with no additional false-positives using the stimulated renin test. For quantitative renography the highest accuracy was for DTPA RU parameter (56%, n = 57) with three technical failures and only one false-positive. Therefore, strict quantitative rules offered no significant improvement over qualitative evaluation for either DTPA or OIH in this population.

The stimulated renin test alone had an accuracy of 58% (n = 57) with three false-positive exams, comparable to CR. However, three false-positive exams among the Group I subjects using this procedure contrasted with zero false-positive captopril renograms. Inadequate specificity of this procedure has been reported by others as well and has long been the bane of testing diseases of low prevalence. Of course, none of the subjects in Group I underwent angiography and the probability

of renovascular disease is, therefore, not zero. However, given the mildness of the hypertension in this group, the probability of renovascular disease in this group is less than 0.1%, according to the Hypertension Detection and Follow-Up Program (*9*).

This study provided only limited data to address the important distinction between the prediction of RVH and RAS. Only 13 subjects underwent PTCA with sufficient follow-up information to evaluate for RVH. The data confirmed the results of the broader study. The measure of CR is not its ability to confirm RAS but to predict improvement or cure of hypertension after renovascular surgical intervention. Setaro et al. (*18*), Dondi et al. (*20*) and others have demonstrated CR's ability in this regard for intervals up to 1 yr after surgery.

In our protocol, a marginal advantage of OIH to DTPA was not statistically significant. The literature also has not distinguished any important diagnostic advantage comparing tubular versus glomerular tracers. We did not study ^{99m}Tc-MAG3 because it was not commercially available at the initiation of our study, and the use of ^{131}I-OIH was necessary to accomplish simultaneous examination of tubular and glomerular tracers. Other literature supports the likelihood that similar tubular properties of MAG3 predict similar behavior clinically (*21,22*). Our results do not exclude the possibility that MAG3, with high tubular extraction and the superior ^{99m}Tc label, is better than either DTPA or OIH.

Recommendations for CR are best categorized according to referral patterns. In populations in which experience suggests a low prevalence of renovascular disease, minimizing false-positive exams gains paramount importance. Captopril renography with either a tubular or glomerular tracer is recommended. Quantitative or qualitative criteria may be used for diagnosis.

In patients with substantial renal dysfunction (e.g., a GFR of <50 ml/min), one should expect a high proportion of abnormal-ND studies. In these exams, the captopril test (stimulated plasma renin assay) may be used adjunctively with qualitative criteria to improve the true-positive rate for OIH and DTPA without introducing false-positive results.

In populations with a high prevalence of RVH, the above strategy again may be applied. However, strategies which enhance sensitivity may be suitable in such populations and are preferred by some investigators (*6*). For example, in Group II, one may assign all abnormal-ND results as positive studies. In Table 2, 39 true-positive OIH studies (38 for DTPA) would result from this approach. Together with 12 true-negative studies, the exam's accuracy would improve to 85% (n = 60). This strategy, therefore, improves sensitivity, but at the expense of specificity because there are now six false-positive results (seven for DTPA). Other diagnostic approaches (*6*) may also have merit, depending on the tolerance for false-positive or false-negative results.

CONCLUSION

Captopril renography has been used to evaluate RAS and its relation to RVH. This investigation, in a prospective fashion:

1. Compared glomerular and tubular tracers directly, resulting in statistical indistinguishability of DTPA and OIH;
2. Compared quantitative and qualitative diagnostic methods, and no statistical differences were found;
3. Explored the range of expected renographic findings among subjects with essential hypertension, a disorder of much greater prevalence; and
4. Established study limitations in a referred population with a high prevalence of renal dysfunction.

The utility of CR and, particularly, its high specificity have been confirmed. False-positive exams among essential hypertensive individuals with good renal function are very uncommon. However, the accuracy of CR in individuals with reduced renal function or bilateral disease is much lower than in those with preserved function or unilateral pathology. No statistical differences are found between DTPA and OIH in subjects either with or without renal dysfunction.

ACKNOWLEDGMENTS

Grant support was provided by the National Heart, Lung and Blood Institute (NHLBI) 5RO1 HL40566, with additional support from NHLBI 5RO1 HL30163. We would like to acknowledge the valued support and helpful comments, especially in the early development of this study, of Gerald Rottman, MD, Salil Sarkar, MD, Michael Middleton, MD, Marlene Rackson, MD, and David Becker, MD.

REFERENCES

1. Fommei E, Ghione S, Palla L, et al. Renal scintigraphic captopril test in the diagnosis of renovascular hypertension. *Hypertension* 1987;10:212–220.
2. Sfakianikis GN, Bourgoignie JJ, Jaffe D, et al. Single dose captopril scintigraphy in the diagnosis of renovascular hypertension. *J Nucl Med* 1987;28:1383–1392.
3. Geyskes GG, Oei HY, Puylaert BAJ, et al. Renovascular hypertension identified by captopril-induced changes in the renogram. *Hypertension* 1987;9:451–458.
4. Dondi M, Franchi R, Levorato M, et al. Evaluation of hypertensive patients by means of captopril-enhanced renal scintigraphy with technetium-99m DTPA. *J Nucl Med* 1989;30:615–621.
5. Hovinga TKK, de Jong PE, Piers DA, et al. Diagnostic use of angiotensin converting enzyme inhibitors in radioisotope evaluation of unilateral renal artery stenosis. *J Nucl Med* 1989;30:605–614.
6. Mann SJ, Pickering TG, Sos TA, et al. Captopril renography in the diagnosis of renal artery stenosis: accuracy and limitations. *Am J Med* 1991;90:30–40.
7. Fommei E, Ghione S, Hilson AJW, et al. Captopril radionuclide test in renovascular hypertension: a European multicentre study. *Eur J Nucl Med* 1993;20:617–623.
8. Fine EJ, on behalf of the Albert Einstein College of Medicine/Cornell University Medical Center Collaborative Hypertension Group. Captopril scintirenography: a protocol to assess efficacy and methodology. A collaborative study. In: Blaufox MD, Hollenberg NK, Raynaud C, eds. *Radionuclide in nephro-urology: contributions in nephrology*, vol. 79. Basel: Karger; 1990:211–218.
9. Lewin A, Blaufox MD, Castle H, Entwisle G, Langford H, on behalf of the Hypertension Detection and Follow-up Program. Apparent prevalence of curable hypertension in the Hypertension Detection and Follow-Up Program. *Arch Intern Med* 1985;145:424–427.
10. Davis BRK, Blaufox, MD, Hawkins CM, et al., for the TAIM Research Group Trial of Antihypertensive Interventions and Management. Design, methods, and selected baseline results. *Controlled Clin Trials* 1989;10:11–30.
11. Russell CD, Bischoff PG, Kontzen FN, et al. Measurement of glomerular filtration rate: single injection plasma clearance method without urine collection. *J Nucl Med* 1985;26:1243–1247.
12. Tauxe WN, Dubovsky EV, Kidd T, et al. New formulas for the calculation of effective renal plasma flow. *Eur J Nucl Med* 1982;7:51–54.
13. Muller FB, Sealey JE, Case DB, et al. The captopril test for identifying renovascular disease in hypertensive patients. *Am J Med* 1986;80:633–644.
14. Fine EJ, Blaufox MD, on behalf of the Einstein/Cornell Collaborative Hypertension Group. The Einstein/Cornell Collaborative protocol assesses efficacy and methodology in captopril scintigraphy. *Am J Hypertension* 1991;4(suppl):716S–720S.
15. Nally JV Jr, Chen C, Fine E, et al. Diagnostic criteria of renovascular hypertension with captopril renography. Consensus statement. *Hypertension* 1991;4(suppl):749S–752S.
16. Zar JH. *Biostatistical analysis*. Englewood Cliffs, NJ: Prentice-Hall; 1974:63–65.
17. Taylor A Jr, Nally J, Aurell M, et al. Consensus report on ACE inhibitor renography for the detection of renovascular hypertension. *J Nucl Med* 1996;37:1876–1882.
18. Setaro JF, Saddler MC, Chen CC, et al. Simplified captopril renography in diagnosis and treatment of renal artery stenosis. *Hypertension* 1991;18:289–298.
19. Fommei, Ghione S, Hilson AJW, et al. Captopril radionuclide test in renovascular hypertension: European multicentre study. *Eur J Nucl Med* 1993;20:617–623.
20. Dondi M, Fanti S, De Fabritiis A, et al. Prognostic value of captopril renal scintigraphy in renovascular hypertension. *J Nucl Med* 1992;33:2040–2044.
21. Dondi M. Captopril renal scintigraphy with ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) for detecting renal artery stenosis. *Am J Hypertension* 1991;4(suppl):737S–740S.
22. Taylor A Jr, Eshima D. Renal artery stenosis and ischemia. Effect on renal blood flow and extraction fraction hypertension. 1994;23:96–103.